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(21) International Application Number: PCT/US96/02080 (22) International Filing Date: 14 February 1996 (14.02.96) (30) Priority Data: 08/388,878 15 February 1995 (15.02.95) US (71) Applicant: NANOSYSTEMS L.L.C. [US/US]; Building 1, 1250 South Collegeville Road, Collegeville, PA 19426 (US). (72) Inventors: RUDDY, Stephen, B.; 226 Stallion Lane, Schwenksville, PA 19473 (US). EICKHOFF, W., Mark; 1313 Rhode Island Circle, Downingtown, PA 19335 (US). LIVERSIDGE, Gary; 258 Colwyn Terrace, West Chester, PA 19380 (US). (74) Agents: WEST, Paul, B.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: SITE-SPECIFIC ADHESION WITHIN THE GI TRACT USING NANOPARTICLES STABILIZED BY HIGH MOLECULAR WEIGHT, LINEAR POLY (ETHYLENE OXIDE) POLYMERS (57) Abstract Nanoparticulate crystalline therapeutic or diagnostic substances formulated with stabilizers and high molecular weight, linear poly (ethylene oxide) polymers, enhance contact between the crystalline therapeutic or diagnostic substances and the gastrointestinal tract providing site-specific and extended therapeutic or diagnostic effect.		

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SITE-SPECIFIC ADHESION WITHIN THE GI TRACT USING
NANOPARTICLES STABILIZED BY HIGH MOLECULAR WEIGHT,
LINEAR POLY (ETHYLENE OXIDE) POLYMERS

5

Field of the Invention

The present invention relates to therapeutic and
diagnostic formulations for gastrointestinal agents in
combination with high molecular weight, linear
10 poly(ethylene oxide) polymers.

Background of the Invention

In the delivery of certain slightly water-soluble
drugs intended to act by contact with the mucosal
15 surface of the gastrointestinal tract (hereinafter
referred to as the GI tract) without substantial
absorption therethrough into the blood stream, the
problem of insufficient adherence and dwell time are
often encountered. Drugs, such as antacids,
20 antimicrobial and antifungal agents tend to pass
through the GI tract without providing sufficient local
preventive/active effects.

Accordingly, there is a need to provide oral GI
formulations that are safe, efficacious and have
25 sufficient dwell or contact time with the GI mucosa.
Such formulations should have excellent mucosal coating
properties for both the upper and lower GI tract, i.e.,
they should have mucoadhesive or bioadhesive properties
that enable the entire GI tract to be coated. There
30 also exists a need to provide formulations to specific
regions within the GI tract. Since the slightly water-
soluble drugs do not by themselves possess such
bioadhesive or mucoadhesive properties, the
formulations containing them must provide the same.

35 The identification of surface active stabilizers
with bioadhesive or mucoadhesive properties that enable
coating of the entire GI tract or specific regions

within the GI tract with therapeutic agents has not been reported to date.

It is common medical practice to employ barium sulfate formulations to image the GI tract of patients.

5 Barium sulfate can be given either orally or rectally to visualize the stomach and small intestine or rectally to visualize the large intestine. Barium sulfate is usually administered as a suspension that has limited stability even with the addition of

10 stabilizers. As such, it often forms clumps that yield resultant radiopaque areas on X-ray films and provides for poor patient acceptability characteristics. Poor patient acceptability characteristics include palatability, patient discomfort during and after

15 administration and prolonged constipation of the patient. Barium sulfate also shows poor affinity for coating the GI mucosa and consequently the patient is often manipulated or rotated to ensure the barium sulfate suspensions coat the gastric mucosa.

20 Nevertheless, segments of the GI tract are often obscured or are not adequately coated, necessitating repeated examinations to achieve satisfactory imaging results.

Bioadhesion is usually achieved by interaction of

25 either a synthetic or natural polymeric substance with the mucosal membranes of the GI tract. Such technology has been employed to enhance drug delivery by increasing the transit time of a drug substance in the GI tract and hence promoting an opportunity for

30 enhanced absorption. With regard to the development of water insoluble or poorly water-soluble drug formulations intended to coat the GI tract, it is important to identify mucosal adhesives that coat the GI surfaces and affect diseased or abnormal tissues.

35 Highly charged carboxylated polyanions are good candidates for use as bioadhesives in the GI tract. See, for example: Park, K. and Robinson, J.R.,

Bioadhesion: Polymers for Orally Controlled Drug Delivery; Method to Study Bioadhesion. Int. J. Pharm., 19, 107 (1984). The formation of a bioadhesive bond between a polymeric substance and the mucosal lining of the GI tract can be visualized as a two step process, i.e., initial contact between the two surfaces and the formation of secondary bonds due to non-covalent interactions. Bioadhesives specific for the GI tract must interact with the mucus layer during attachment.

Mucus, a general term for the heterogeneous secretion found on epithelial surfaces of the GI tract, is made of the following components: glycoprotein macromolecules, inorganic salts, proteins, lipids, and mucopolysaccharides. These glycoproteins typically consist of a protein core with carbohydrate side chains. This forms a network of mucus that is a continuous layer covering the GI tract. From a bioadhesive perspective, mucus consists of highly hydrated, cross linked linear, flexible yet random coiled glycoprotein molecules with a net negative charge. Understanding the principals of bioadhesion is the basis for formulating oral or rectal compositions for coating portions of the GI tract. Bioadhesion accounts for the interaction between a biological surface and a biological substance. As noted previously, bioadhesive agents are usually polymeric substances that adhere to tissues by ionic or covalent bonds or by physical attachment. Several theories of bioadhesion have been published including electronic, adsorption, wetting, diffusion, and fracture theories. Bioadhesives bind to membrane surfaces and are retained for various periods of time.

We have discovered a certain class of polymers for promoting site specific bioadhesion or mucoadhesion within the GI tract. The polymers provide for site-specific delivery of medicinal agents within the GI

tract. Moreover, the polymers provide for site-specific imaging of the GI tract.

In accordance with the present invention, there is provided an orally/rectally administrable GI
5 formulation containing an effective amount of a water-insoluble or poorly water-soluble therapeutic agent. There is further provided a method for affecting diseased conditions in the GI tract comprising oral or rectal administration to a patient, an effective amount
10 of the above-identified formulation to prevent or cure such diseased conditions. There is further provided a method and formulation for X-ray diagnostic imaging of the GI tract which includes orally or rectally administering to the patient an effective amount of X-
15 ray contrast compositions.

Summary of the Invention

In accordance with the present invention, there is provided an orally/rectally administrable therapeutic
20 composition or diagnostic composition comprising:

of from about 0.1% to about 45% w/v of an essentially water-insoluble particulate drug or diagnostic agent having an effective average particle size of less than about 2000 nm, more preferably an
25 effective average particle size of less than about 1000 nm, and most preferably an effective average particle size of less than about 400nm;

of from about 0.1 to about 10.0% w/v, and preferably of from about 1 to about 6% w/v of a
30 bioadhesive stabilizer;

of from about 0.1% to about 5.0% w/v of a long chain linear poly (ethylene oxide) polymer having a molecular weight of from about 100,000 to about 2,000,000 daltons;

35 water to make 100% w/v.

Secondary stabilizers may also be used in the formulations up to about 1% w/v, preferably up to about

0.2% w/v, and most preferably up to about 0.1% w/v. Secondary stabilizers include dioctylsulfosuccinate (DOSS) and sodium laury sulfate (SLS).

Other ingredients customarily used in oral pharmaceutical or diagnostic formulations may also be included, such as flavorants, colorants and preservatives to provide pharmaceutically acceptable and palatable formulations.

10 Description of the Preferred Embodiment

The present invention is the employment of nanoparticles of drug substance stabilized by long chain polyethyleneoxides (PEOs), the latter of which may serve as a bioadhesive agent through physical and chemical interaction with the mucus or mucosal surfaces within the GI tract. It has been shown that incorporation of linear PEOs having a molecular weight of approximately 100,000-2,000,000 into a formulation of nanoparticulate barium sulfate resulted in prolonged retention of the radiopaque in the stomach and duodenum and/or superior coating in the ascending, transverse and descending colon of beagle dogs.

Nanoparticles, described in U.S. Patent No. 5,145,684, are particles consisting of a poorly soluble therapeutic or diagnostic agent onto which are adsorbed a non-cross linked surface modifier, and which have an average particle size of less than about 400 nanometers (nm). As used herein poorly soluble means that the material has a solubility in aqueous medium of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. Suitable drug substances for use in the present invention are detailed below.

Suitable drug substance can be selected from a variety of known classes of drugs, for example, antacids, anti-inflammatory agents, antibiotics (including penicillins), antimycobacterial agents, antiviral agents, corticosteroids,

parasympathomimetics, demulcents, emollients,
gastrointestinal protectives and adsorbents,
antifungals, H₂-blocking agents, proton pump
inhibitors, muscarinic antagonists, bismuth compounds,
5 sucralfate, carbenoxolone, prostaglandins, digestants,
bile acids, laxatives, antiparasitic agents,
anthelmintics, antiprotozoal agents, antimicrobial
agents, vitamins, immunologic agents, vaccines,
anesthetics, lipid-regulating agents and bile acid
10 sequestrants. Preferred drug substances include those
intended for oral administration or rectal
administration. A description of these classes of
drugs and a listing of species within each class can be
found in Martindale, The Extra Pharmacopoeia, Twenty-
15 Ninth Edition, The Pharmaceutical Press, London, 1989.
The drug substances are commercially available and/or
can be prepared by techniques known in the prior art.

Surfactants found to have bioadhesive or
mucoadhesive properties include:

- 20 1) Poloxamers which are polyethylene-polypropylene
oxide tri-block co-polymers of the formula
(polyethylene oxide)_a-(polypropylene oxide)_b-
(polyethylene oxide)_c wherein
a is 46, 52, 62, 75, 97, 98, 122, and 128;
25 b is 16, 30, 35, 39, 47, 54, and 67; and
c is 46, 52, 62, 75, 97, 98, 122, and 128;
2) polyvinyl alcohol,
3) polyvinyl pyrrolidone,
4) hydroxypropyl methylcellulose, and
30 5) polyoxyethylene sorbitan mono-oleate (Tween
80).

The particles can be prepared in a method
comprising the steps of dispersing a therapeutic or
diagnostic agent in a liquid dispersion medium and
35 applying mechanical means in the presence of grinding
media to reduce the particle size of the therapeutic or
diagnostic agent to an effective average particle size

of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

5 As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk
10 centrifugation. When photon correlation spectroscopy (PCS) is used as the method of particle sizing the average particle diameter is the Z-average particle diameter known to those skilled in the art. By "an effective average particle size of less than about 400
15 nm" it is meant that at least 90% of the particles have a weight average particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments, the effective average particle size is less than about 300 nm and more preferably less
20 than about 250 nm. In some embodiments, an effective average particle size of less than about 100 nm has been achieved. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a
25 particle size less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 400 nm. In some embodiments, essentially all of the particles have a size less than 250 nm.

30 The therapeutic or diagnostic agent selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse therapeutic or diagnostic agent selected be
35 less than about 100 μ m as determined by sieve analysis. If the coarse particle size of the therapeutic or diagnostic agent is greater than about 100 μ m, then it

is preferred that the particles of the therapeutic or diagnostic agent be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

5 The mechanical means applied to reduce the particle size of the therapeutic or diagnostic agent conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such
10 as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size.

 The grinding media for the particle size reduction
15 step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles with shorter processing times and impart less
20 wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. We have found that zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, glass, and polymeric grinding media provide particles
25 having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. However, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful.

30 The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less
35 than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the therapeutic or diagnostic agent. Processing temperatures of less than about 30 - 40°C are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Control of the temperature, e.g., by jacketing or immersion of the milling chamber in ice water are contemplated. Processing pressures from about 1 psi (0.07 kg/cm²) up to about 50 psi (3.5 kg/cm²) are contemplated. Processing pressures from about 10 psi (0.7 kg/cm²) to about 20 psi (1.4 kg/cm²) are typical.

Examples

In order to assess the efficiency of mucosal coating throughout the GI tract, nanoparticle formulations of barium sulfate (15% w/v) were prepared in the presence of various polymeric stabilizers and administered (10 ml/kg) to anesthetized beagle dogs via gastric tubation. At 15 minutes post-dose, an equivalent volume of air was administered in order to create a double contrast effect. Animals were then placed in the dorsal recumbent position after which radiographs of the GI tract were generated (15, 30, 45, 60, 120, 240 minutes post-dose) following ventral-dorsal X-ray exposure. Resulting radiographs were developed and evaluated in order to determine the persistence of coating throughout the GI tract.

Resulting radiographs revealed an unexpected synergy between polymeric stabilizers (linear, high molecular weight, polyethylene oxide polymers [PEO's] and ethylene oxide-propylene oxide tri-block co-

polymers (poloxamers)) as indicated by the retention of nanoparticulate material in the extreme upper GI tract (i.e., stomach and descending duodenum) and/or the colon for prolonged periods. Such efforts were not realized; however, in the case of poloxamers alone, which provided for excellent overall coating of the GI tract throughout much of the small intestine, while demonstrating limited ability to coat the regions specified above. Moreover, employment of PEO's alone did not result in suitable particle size reduction, a factor which had previously been shown to be of paramount importance in promoting adhesion of particulate material to the mucosal surfaces of the GI tract.

The poly(ethylene oxide) polymers are non-ionic water soluble resins. They are available from Union-Carbide in a wide variety of molecular weights. In the present invention molecular weights over 2,000,000 for PEO's are not effective as the resulting composition is too viscous to administer. The poloxamers are available from Pluronic and have molecular weight less than 20,000. The poloxamers are shown by the manufacturer-designated number.

Tables I and II illustrate the persistence of mucosal coating in the vicinity of the stomach and descending duodenum in the presence and absence of PEO's. Resulting radiographs were evaluated in accordance with the following grading scheme:

Stomach and Duodenum

+++ indicates extensive coating of the stomach and/or descending duodenum

++ indicates moderate coating of the stomach and/or descending duodenum

+ indicates minor coating of the stomach and/or descending duodenum

- indicates absence of coating of the stomach and/or descending duodenum

Colon

+++ Indicates coating of the ascending,
transverse and descending colon

++ Indicates coating of 2/3 of the colon

5 + Indicates coating of 1/3 of the colon

- Indicates absence of coating of the colon.

Table I

10 Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation
Stabilized by 4% w/v Pluronic F108

Coating Efficiency

15

Time (min)	Stomach		Duodenum		Colon	
	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	+++	++	+++	-	-
30	+++	+++	+	++	-	-
45	+++	+++	+	++	-	-
60	++	+++	+	+	-	-
120	+	++	-	+	-	+
240	-	-	-	-	++	++

Tabl II

Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation
Stabilized by 3% w/v Pluronic F108 and 1% w/v POLYOX WSRN-750

5

Coating Efficiency

Time (min)	Stomach		Duodenum		Colon	
	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	n/a	+++	n/a	-	n/a
30	+++	n/a	+++	n/a	-	n/a
45	+++	n/a	+++	n/a	-	n/a
60	+++	n/a	+++	n/a	-	n/a
120	++	n/a	-	n/a	-	n/a
240	+	n/a	-	n/a	-	n/a

*n/a indicates that data is not available

10

These examples demonstrate clearly that persistence of mucosal coating is prolonged in the upper regions of the small intestine when barium sulfate nanoparticles are stabilized by both Pluronic F108 and POLOX WSNR-750, particularly at time points in excess of 45 minutes. Such effects are further evidenced by the delayed appearance of nanoparticulate material in the colon, consistent with a longer residence time in the small bowel. Similar results were obtained when a blend of Pluronic F127 and POLOX WSNR-750 was utilized to promote site-specific adhesion of barium sulfate nanoparticles to the stomach and duodenum (see Tables III and IV).

20

Table III
Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation
Stabilized by 4% w/v Pluronic F127

5

Coating Efficiency

	Stomach		Duodenum		Colon	
Time (min)	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	+++	++	+	-	-
30	+++	+++	+	+	-	-
45	+++	+++	-	+	-	-
60	++	++	-	-	-	-
120	+	++	-	-	++	++
240	-	-	-	-	++	+

10

Table IV
Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation
Stabilized by 3% w/v Pluronic F127 and 1% w/v POLYOX WSRN-750

Coating Efficiency

15

	Stomach		Duodenum		Colon	
Time (min)	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	+++	+++	+++	-	-
30	+++	+++	++	++	-	-
45	+++	+	++	++	-	-
60	+++	+	++	++	-	-
120	++	+	++	++	-	-
240	-	-	-	-	++	+

In the case of Pluronic F98 and POLOX WSNR-750; however, a slightly different effect was realized. While combination of polymers resulted in prolonged retention of barium sulfate nanoparticles in the

20

stomach, a comparatively weak effect was observed in the descending duodenum, where only a moderate improvement in mucoadhesion was achieved. However, the combination later provided for improved mucoadhesion in the colonic region of the same animals as evidenced by extensive coating of the ascending, transverse and descending colonic loops of both animals at 4 hours post administration.

10

Table V

Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation Stabilized by 4% w/v Pluronic F98

Coating Efficiency

15

Time (min)	Stomach		Duodenum		Colon	
	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	+++	-	+	-	-
30	n/a	++	n/a	+	n/a	-
45	+	++	-	-	-	-
60	+	+	-	-	-	-
120	+	-	-	-	++	+
240	-	-	-	-	+	++

*n/a indicates that data is not available

Table VI
Coating Efficiency of a 15% w/v Nanoparticulate Barium Sulfate Formulation
Stabilized by 3% w/v Pluronic F98 and 1% w/v POLYOX WSRN-750

5

Coating Efficiency

Time (min)	Stomach		Duodenum		Colon	
	Subject A	Subject B	Subject A	Subject B	Subject A	Subject B
15	+++	+++	-	++	-	-
30	+++	+++	-	++	-	-
45	+++	+++	-	+	-	-
60	++	+++	-	+	-	-
120	++	+++	-	-	+++	++
240	-	+	-	-	+++	+++

10

In the examples described above it is apparent that site-specificity can be altered by adjusting the type and amount of PEO and poloxamer. Thus, a therapeutic formulation can be delivered in a site specific manner to the stomach, duodenum or colon.

15

While there has been shown and described what are at present considered to be the preferred embodiments of the present invention, various alterations and modifications may be made herein. All such modifications are intended to be included within the scope of the appended claims.

20

What is Claimed is:

1. An orally/rectally therapeutic formulation comprising:

- 5 of from about 0.1% to about 45% w/v of an essentially water-insoluble particulate drug having an effective average particle size of less than about 2000 nm;
- 10 of from about 0.1 to about 10.0% w/v of a bioadhesive polymeric stabilizer selected from the group consisting of: polyethylene-polypropylene oxide tri-block co-polymers of the formula;
- (i) (polyethylene oxide)_a-(polypropylene oxide)_b-(polyethylene oxide)_c wherein
- 15 a is 46, 52, 62, 75, 97, 98, 122, and 128;
b is 16, 30, 35, 39, 47, 54, and 67; and
c is 46, 52, 62, 75, 97, 98, 122, and 128;
- (ii) polyvinyl alcohol,
- (iii) polyvinyl pyrrolidone,
- 20 (iv) hydroxypropyl methylcellulose, and
(v) polyoxyethylene sorbitan mono-oleate;
- of from about 0.1% to about 5.0% w/v of a long chain linear poly (ethylene oxide) polymer having a molecular weight of from about 100,000 to about
- 25 2,000,000 daltons;
water to make 100% w/v.

2. The therapeutic formulation of claim 1 wherein said drug is selected from the group consisting of:
- 30 antacids, anti-inflammatory agents, antibiotics, antimycobacterial agents, antiviral agents, corticosteroids, parasympathomimetics, demulcents, emollients, gastrointestinal protectives and adsorbents, antifungals, H₂-blocking agents, proton
- 35 pump inhibitors, muscarinic antagonists, bismuth compounds, sucralfate, carbenoxolone, prostaglandins, digestants, bile acids, laxatives, antiparasitic

agents, anthelmintics, antiprotozoal agents, antimicrobial agents, vitamins, immunologic agents, vaccines, anesthetics, lipid-regulating agents and bile acid sequestrants.

5

3. The therapeutic formulation of claim 1 wherein the effective average particle size is less than about 1000 nm.

10

4. The therapeutic formulation of claim 1 wherein the effective average particle size is less than about 400 nm.

15

5. An orally/rectally gastrointestinal diagnostic X-ray formulation comprising:

of from about 0.1% to about 45% w/v of an essentially water-insoluble particulate radiopaque crystalline material having an effective average particle size of less than about 2000 nm;

20

of from about 0.1 to about 10.0% w/v of a bioadhesive polymeric stabilizer selected from the group consisting of: polyethylene-polypropylene oxide tri-block co-polymers of the formula;

(i) (polyethylene oxide)_a-(polypropylene oxide)_b-(polyethylene oxide)_c wherein

a is 46, 52, 62, 75, 97, 98, 122, and 128;

b is 16, 30, 35, 39, 47, 54, and 67; and

c is 46, 52, 62, 75, 97, 98, 122, and 128;

30

(ii) polyvinyl alcohol,

(iii) polyvinyl pyrrolidone,

(iv) hydroxypropyl methylcellulose, and

(v) polyoxyethylene sorbitan mono-oleate;

of from about 0.1% to about 5.0% w/v of a long chain linear poly (ethylene oxide) polymer having a molecular weight of from about 100,000 to about 2,000,000 daltons;

35

water to make 100% w/v.

6. The orally/rectally administrable gastrointestinal diagnostic X-ray contrast formulation of claim 5 wherein said radiopaque crystalline material is selected from the group consisting of: 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid ethyl ester (WIN 05316), 2-(3,5-Bis-acetylamino-2,4,6-triiodo-benzyloxy)-2-methyl malonic acid (WIN 67975), propanedioic acid, [[3,5-Bis-(acetylamino)-2,4,6-triiodo-benzyl]oxy]-bis(1-methylethyl) ester acid ethyl ester (WIN 68165), Diethyl 5-acetylamino-2,4,6-triiodo-isophthalate (WIN 59316), ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate (WIN 8883), bis-[1-(ethoxycarbonyl)propyl]-2,4,6-triiodo-5-acetylamino-isophthalate (WIN 68183), 1,3,5-triethyl-2,4,6-triiodobenzene (WIN 68756), 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid 4-methoxy-benzyl ester (WIN 67754), 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid 4-isopropyl benzoate ester (WIN 67956), (6-ethoxy-6-oxohexyl 3,5-bis(acetylamino)2,4,6-triiodobenzoate (WIN 67722), and 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid 5-isopropoxycarbonyl-pentylester (WIN 67995).

7. The orally/rectally administrable gastrointestinal diagnostic X-ray contrast formulation of claim 5 wherein said particulate radiopaque crystalline material is selected from the group consisting of:

barium sulfate, barium hexaborite, barium chromite, barium fluogallate, barium tri-ortho phosphate, barium metasilicate, barium titanate and barium zirconate.

8. The therapeutic formulation of claim 5 wherein the effective average particle size is less than about 1000 nm.

9. The therapeutic formulation of claim 5 wherein the effective average particle size is less than about 400 nm.

- 5 10. The method of carrying out X-ray examination of the gastrointestinal tract of a patient, comprising:
 orally/rectally administering an X-ray contrast composition comprising:
 of from about 0.1% to about 45% w/v of an
10 essentially water-insoluble particulate radiopaque crystalline material having an effective average particle size of less than about 2000 nm;
 of from about 0.1 to about 5.0% w/v of a
15 bioadhesive surfactant stabilizer selected from the group consisting of: polyethylene-polypropylene oxide tri-block co-polymers of the formula;
 (i) (polyethylene oxide)_a-(polypropylene oxide)_b-(polyethylene oxide)_c wherein
 a is 46, 52, 62, 75, 97, 98, 122, and 128;
20 b is 16, 30, 35, 39, 47, 54, and 67; and
 c is 46, 52, 62, 75, 97, 98, 122, and 128;
 (ii) polyvinyl alcohol,
 (iii) polyvinyl pyrrolidone,
 (iv) hydroxypropyl methylcellulose, and
25 (v) polyoxyethylene sorbitan mono-oleate;
 of from about 0.1% to about 5.0% w/v of a long chain linear poly (ethylene oxide) polymer having a molecular weight of from about 100,000 to about 2,000,000 daltons;
30 water to make 100% w/v.

11. The method of carrying out X-ray examination of the gastrointestinal tract of a patient according to claim 10 wherein said X-ray contrast composition is
35 selected from the group consisting of: 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid ethyl ester (WIN 05316), 2-(3,5-Bis-acetylamino-2,4,6-triiodo-

benzyloxy)-2-methyl malonic acid (WIN 67975),
propanedioic acid, [[3,5-Bis-(acetylamino)-2,4,6-
triiodo-benzyl]oxy]-bis(1-methylethyl) ester acid ethyl
ester (WIN 68165), Diethyl 5-acetylamino-2,4,6-triiodo-
5 isophthalate (WIN 59316), ethyl 3,5-bis(acetylamino)-
2,4,6-triiodobenzoate (WIN 8883), bis-[1-
(ethoxycarbonyl)propyl]-2,4,6-triiodo-5-acetylamino-
isophthalate (WIN 68183), 1,3,5-triethyl-2,4,6-
triiodobenzene (WIN 68756), 3,5-Bis-acetylamino-2,4,6-
10 triiodo-benzoic acid 4-methoxy-benzyl ester (WIN
67754), 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic acid
4-isopropyl benzoate ester (WIN 67956), (6-ethoxy-6-
oxohexyl 3,5-bis(acetylamino)2,4,6-triiodobenzoate (WIN
67722), and 3,5-Bis-acetylamino-2,4,6-triiodo-benzoic
15 acid 5-isopropoxycarbonyl-pentylester (WIN 67995).

12. The method of carrying out X-ray examination
of the gastrointestinal tract of a patient according to
claim 10 wherein said particulate radiopaque
20 crystalline material is selected from the group
consisting of barium sulfate, barium hexaborite, barium
chromite, barium fluogallate, barium tri-ortho
phosphate, barium metasilicate, barium titanate and
barium zirconate.

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13. The therapeutic formulation of claim 10
wherein the effective average particle size is less
than about 1000 nm.

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14. The therapeutic formulation of claim 10
wherein the effective average particle size is less
than about 400 nm.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/02080

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/51 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 409 690 (EXSYMOL) 23 January 1991 see claims 1,8 see page 2, line 42 - line 47 see page 4, line 4 - line 23 ---	1-14
A	EP,A,0 499 299 (STERLING WINTHROP) 19 August 1992 see the whole document -----	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

4 July 1996

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Ventura Amat, A

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